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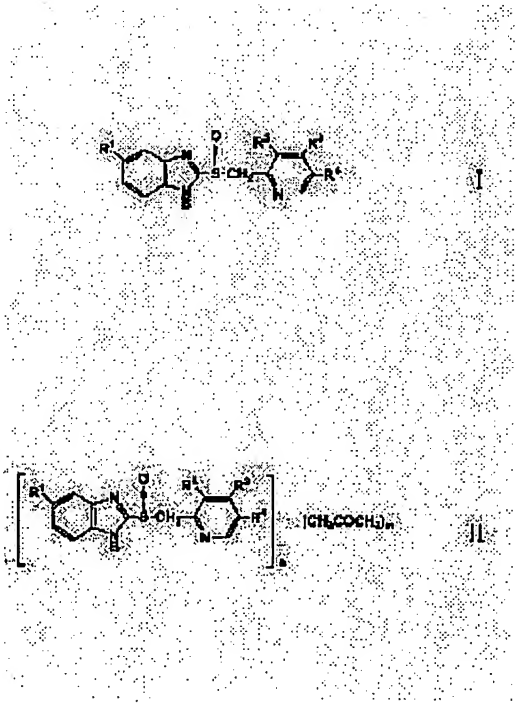
(54) CRYSTAL OF SULFOXIDE DERIVATIVE AND ITS PRODUCTION

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a new crystal of the subject derivative useful as a medicine (an intermediate thereof) such as a gastric acid secretion inhibitor/antiulcerous agent and excellent in pharmaceutical processability and storage stability/ moisture resistance as an original drug or pharmaceutical preparation, by crystallizing the subject derivative so as to have a specific structure.

SOLUTION: This crystal of the subject derivative (salt) is obtained by producing a crystal thereof having a structure of formula I [R1 is H or (difluoro) methoxy; R2 is methyl or methoxy; R3 is 3-methoxypropoxy, methoxy or 2,2,2- trifluoroethoxy; R4 is H or methyl; and B is H, an alkali metal or a 1/2 alkaline earth metal] {e.g. 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfynyl}-1 H-benzimidazole sodium salt crystal}. The crystal of the derivative of formula I (salt) can be produced by, for example, crystallizing an acetone complex of a sulfoxide derivative (salt) of formula II ((n) and (m) are each 1-4) in a lower fatty acid ester.



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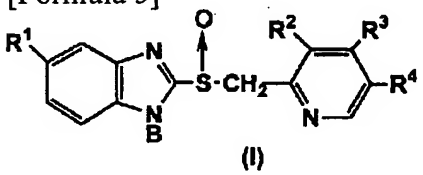
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the new crystal excellent in the pharmaceutical preparation workability of a sulfoxide derivative useful as physic, such as a gastric-acid secretion inhibitor, antiulcer drug, etc. indicated by JP,1-6270,A (example 33), JP,61-50978,A (example 2), JP,54-141783,A (example 21), or JP,61-22079,A (Example 2), or its salt permitted in pharmacology, a bulk drug, or the preservation stability and the moisture resistance of pharmaceutical preparation, and its manufacturing method.
[0002]
[Description of the Prior Art] Conventionally, a sulfoxide derivative or its salt permitted in pharmacology has been manufactured as an amorphous substance (amorphous) or an amorphous solid-state (powder) as indicated by JP,1-6270,A (EP-268956, US-5045552), JP,61-50978,A (EP-174726, US-4628098), JP,54-141783,A (EP-5129, US-4255431), JP,61-22079,A (EP-166287, US-4758579), etc. Therefore, the clear melting point was not shown but was known as a solid-state of the decomposition point or a low-melt point point.
[0003] For example JP,1-6270,A It is 140 to 141 degree C (decomposition). the 2-{[4-(3-methoxy propoxy)-3-methylpyridine-2-IRU] methyl sulfinyl}-1H-benzimidazole sodium salt (Rabeprazole Sodium) of (an example 33) -- melting point; -- 2-{[4-(2, 2, and 2-trifluoroethoxy)-3-methylpyridine-2-IRU] methyl sulfinyl}-1H-benzimidazole of JP,61-50978,A (example 2) (it Lansoprazole(s)) In R1=H, R2=CH3, R3=H, and R4=CH2CF3, it is melting point;178-182 degree C (decomposition). It is 162 degrees C. the 5-methoxy-2-[(4-methoxy -3, 5-dimethyl-2-pyridyl) methyl sulfinyl]-1H-benzimidazole (Omeprazole) of JP,54-141783,A (example 21) -- melting point; -- 5 of JP,61-22079,A (Example 2) -- the - difluoro methoxy-2-[(4, 5-dimethoxy-2-pyridyl) methyl sulfinyl]-1H-benzimidazole (Pantoprazole) -- melting point; -- it was 159 degrees C (decomposition).
[0004]
[Problem(s) to be Solved by the Invention] However, in the drugs by which stability is bad at the time of bulk drug preservation and pharmaceutical manufacturing, or preservation, and a high grade is extremely called for from environmental conditions, such as light, air, humidity, and temperature, at it with the bulk drug of an amorphous substance or an amorphous solid-state, it was a big problem. Furthermore, since the bulk drug of an amorphous substance or an amorphous solid-state had moisture absorption resolvability, the solvent which can be used at the time of pharmaceutical manufacturing was limited to the anhydride, and it had also become the factor which raises pharmaceutical preparation cost.

[0005] Moreover, in the freeze drying method of the bulk drug adopted, for example in JP,1-6270,A (example 33), the production scale was restricted by the capacity and capacity of equipment, and there was a trouble which cannot perform flexible correspondence in production-planning modification of a scale-up, a scale down, etc. Furthermore, with a freeze drying method, water-solution freezing - a vacuum drying took long duration and great energy, and a desirable approach was not necessarily able to

be told to them from a viewpoint of a manufacturing cost or environmental protection.
[0006] Thus, the present condition is that the high grade sulfoxide derivative excellent in pharmaceutical preparation workability, a bulk drug, or the preservation stability and the moisture resistance of pharmaceutical preparation or its salt's existence gestalt permitted in pharmacology is not established yet, and new crystal form and its manufacture approach were searched for.
[0007]
[Means for Solving the Problem] this invention persons have advanced research wholeheartedly aiming at an improvement of the above-mentioned trouble. Consequently, it shows clearly that it is satisfied with a sulfoxide derivative also unexpectedly useful as physic, such as a gastric-acid secretion inhibitor and antiulcer drug, or its salt permitted in pharmacology of all the above-mentioned terms and conditions by using a header and it for the new crystal which was not known until now existing, and came to complete this invention.
[0008] Therefore, this invention offers the new crystal form excellent in the pharmaceutical preparation workability of physic, such as a gastric-acid secretion inhibitor and antiulcer drug, a sulfoxide derivative useful as physic manufacture intermediate field, or its salt permitted in pharmacology, a bulk drug, or the preservation stability and the moisture resistance of pharmaceutical preparation, and its manufacture approach.
[0009] Then, this invention is explained in full detail below. First, the crystal (I) of the sulfoxide derivative concerning this invention or its salt permitted in pharmacology is expressed with the following general formula.
[0010]
[Formula 5]



(I)

[0011] the inside of a formula, and R1 -- a hydrogen atom, a methoxy group, or a difluoro methoxy group -- R3 means 3-methoxy propoxy group, a methoxy group or 2 and 2, and 2-trifluoroethoxy radical, and, as for R4, R2 means a hydrogen atom or a methyl group for a methyl group or a methoxy group, respectively. B means a hydrogen atom, an alkali-metal atom, or 1 / 2 alkaline-earth-metal atom.
[0012] During the here above-mentioned definition, an alkali atom specifically means a sodium atom, a potassium atom, a lithium atom, etc., and although an alkaline-earth-metal atom can specifically mention a calcium atom, a magnesium atom, etc., it is a sodium atom or a magnesium atom more preferably.
[0013] The acetone complexes of rabeprazole (Rabeprazole), lansoprazole (Lansoprazole), omeprazole (Omeprazole), or punt PURAZORU (Pantoprazole) or those salts that are permitted in pharmacology can more specifically as a sulfoxide derivative be mentioned.
[0014] The new crystal (I) of the sulfoxide derivative furthermore applied to this invention or its salt permitted in pharmacology is characterized by absorption in the infrared absorption spectrum in the peak in a powder X diffraction pattern, and/or a potassium bromide.
[0015] as the new crystal (I) of the sulfoxide derivative concerning this invention, or its salt permitted in pharmacology -- more -- concrete -- for example, the crystal of rabeprazole sodium salt -- [the crystal (II) of 2-{[4-(3-methoxy propoxy)-3-methylpyridine-2-IRU] methyl sulfinyl}-1H-benzimidazole sodium salt] can be mentioned. This new crystal is concretely characterized by the characteristic absorption in the infrared absorption spectrum in the peak in the powder X diffraction pattern measured by the following approach, and/or a potassium bromide.
[0016] A powder X diffraction pattern measuring method and conditions (1) The powder X diffraction pattern was measured in the following Measuring conditions per about 100mg of measuring method samples.

(2) Measuring condition Target:CuFilter:monochroVoltage:40KVCurrent:20 mASlit:DS 1, RS 0.15, SS 1Scan speed:2 deg/min.Range:5~30 degree[0017]

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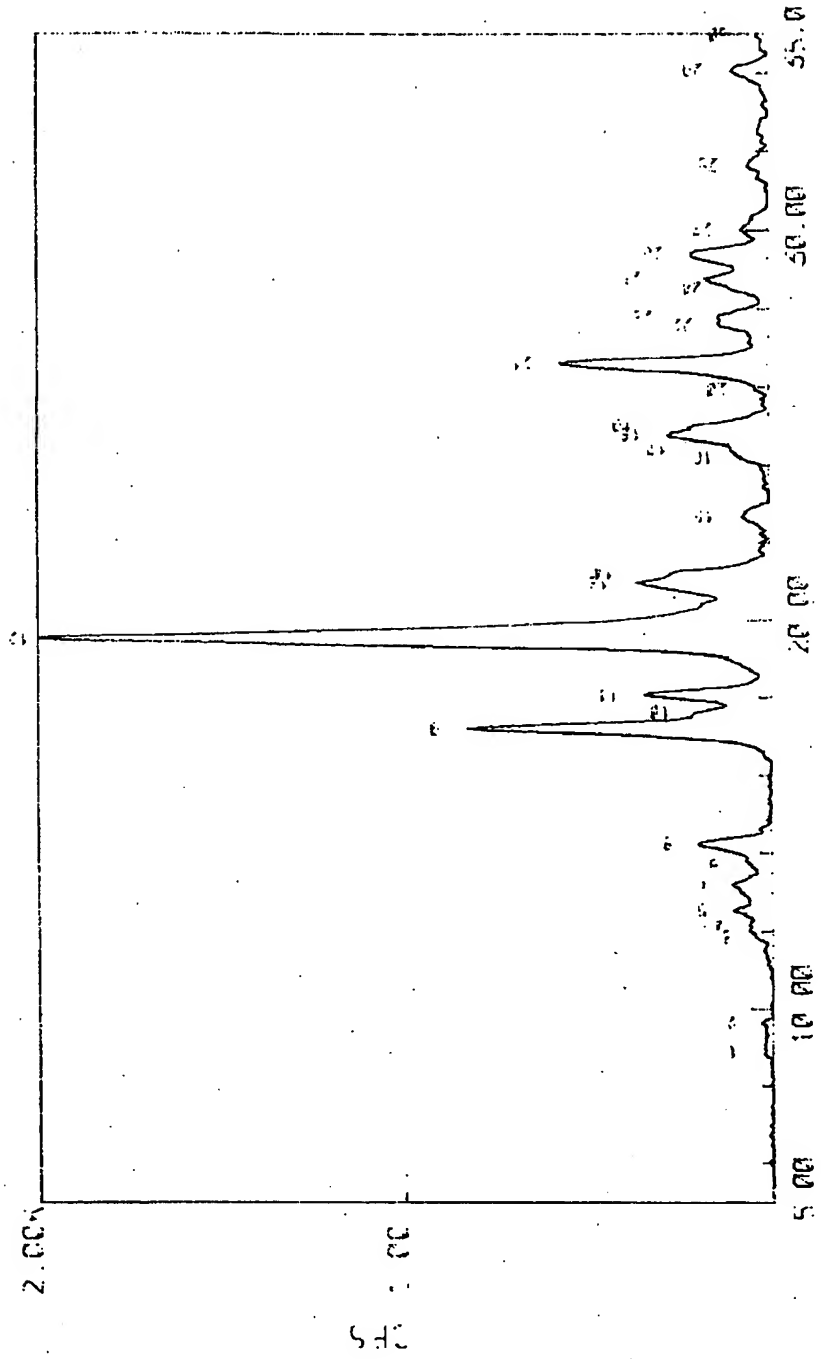
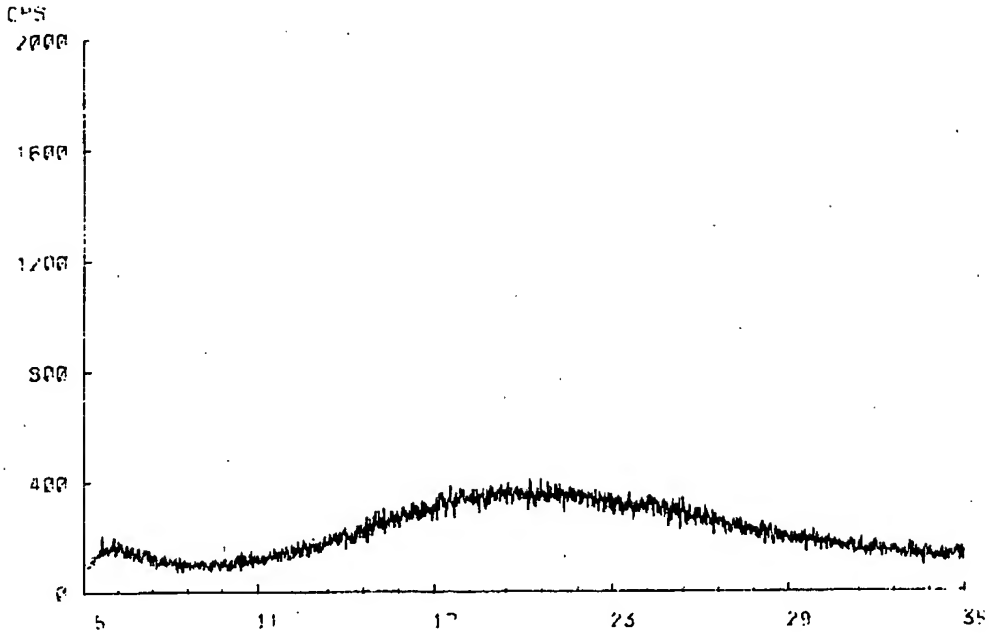
DRAWINGS

[Drawing 1]



[Drawing 2]



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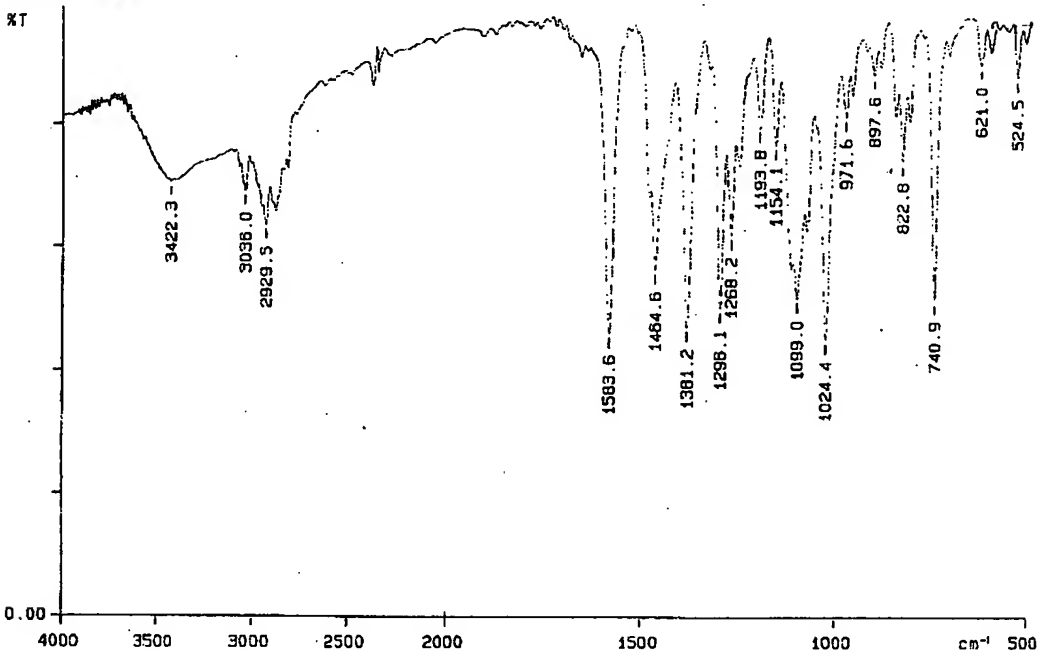

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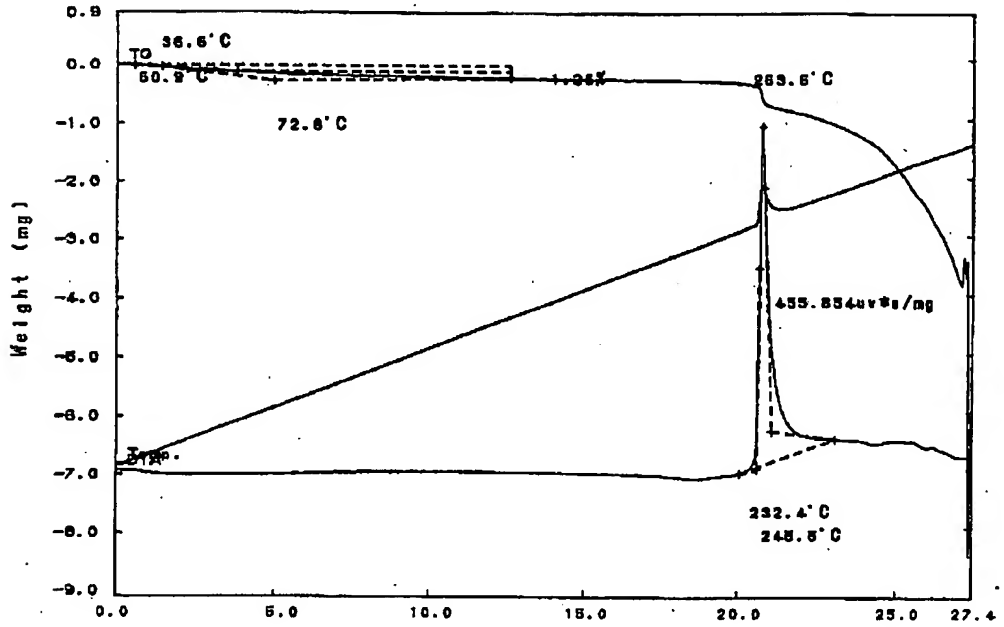

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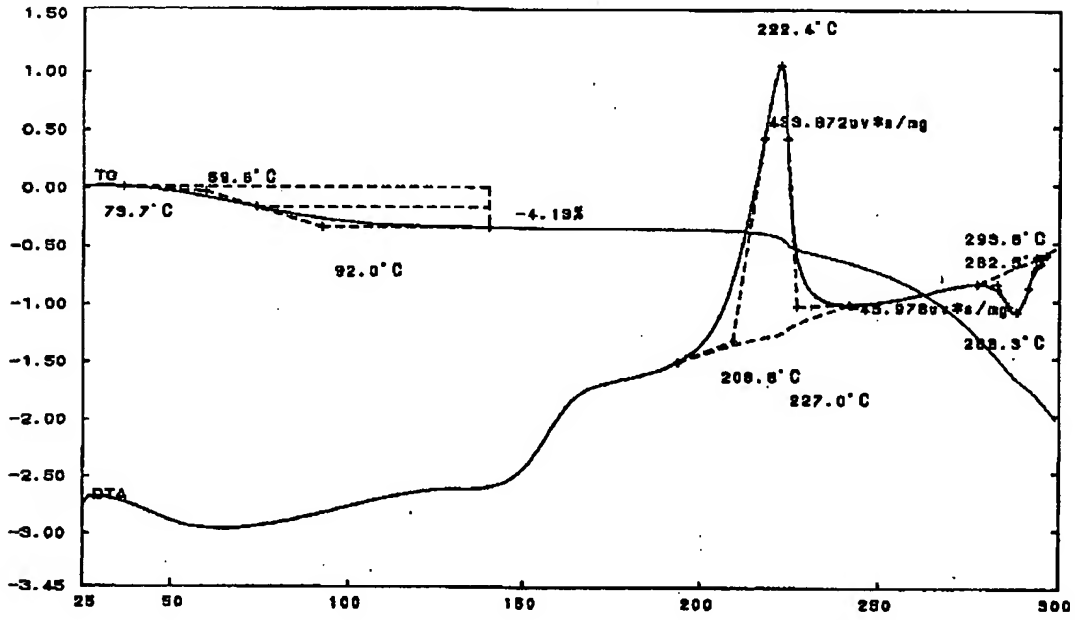

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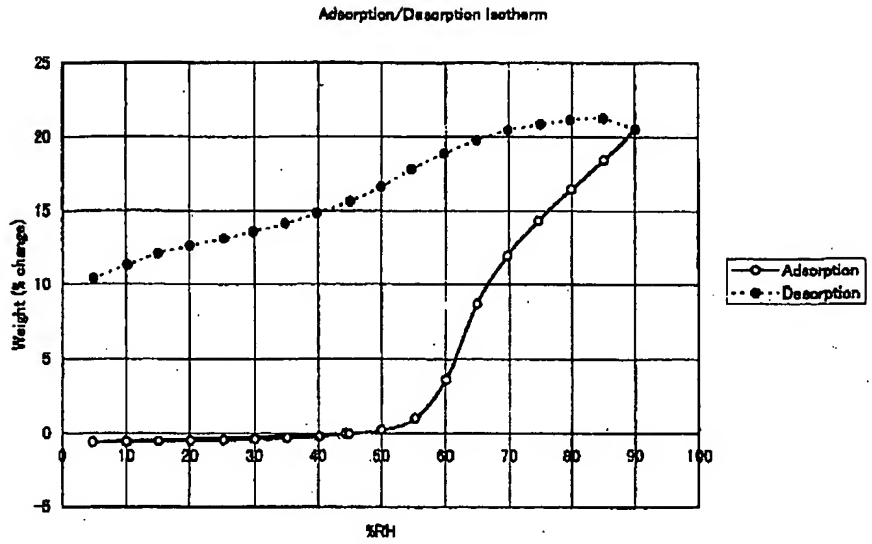
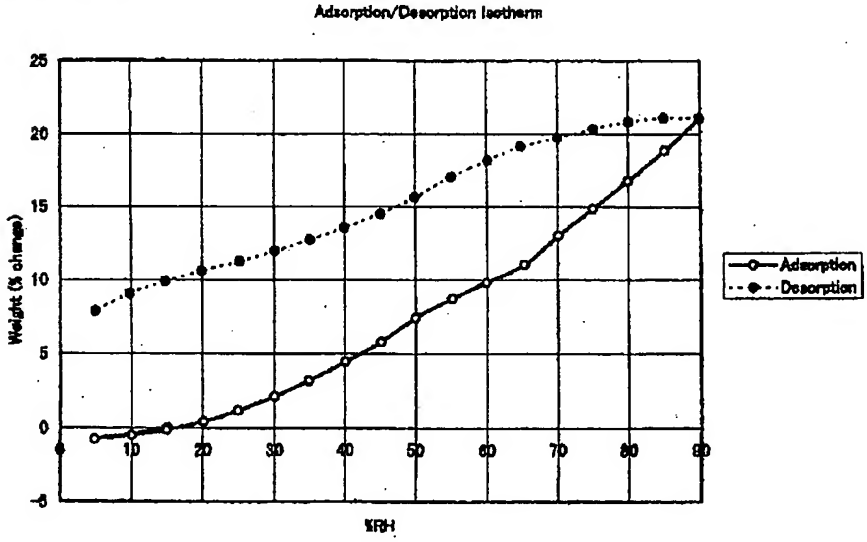


[Drawing 7]



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